

ENVIRON

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Dr. Sue Shallal
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U.S. Environmental Protection Agency, Science Advisory Board (1400F)
1200 Pennsylvania Avenue, NW
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Submitted via hand delivery and e-mail

Re: Docket OPPT docket 2002-0001

Dear Dr. Shallal:

Thank you for the opportunity to provide these comments for review by the EPA Science Advisory Board Committee considering EPA's draft risk assessment for PFOA. I would appreciate your circulating this letter to SAB member as soon as possible.

These comments reflect my own conclusions, but I note for the record that I am familiar with the PFOA dataset and submit these comments because I have been engaged for a number of years to render independent advice to 3M Company regarding its fluorochemical research program and findings. I am a co-author of a peer-reviewed, published risk assessment for PFOA (Butenhoff, et al., "Characterization of Risk for General Population Exposure to Perfluorooctanoate," *Regulatory Toxicology and Pharmacology* 39: 363-380, 2004).¹

I would like to comment on three topics posed for consideration by the SAB panel:

1. MOE Approach and Use of Internal Dose Comparison

EPA has used the margin of exposure (MOE) approach to characterize the potential health risk by dividing the serum PFOA level in experimental animals at the NOAEL or LOAEL by the corresponding PFOA level seen in humans. The magnitude of the MOE gives an indication of whether or not adverse effects are likely to occur in humans – the larger the MOE, the less the potential risk of adverse effects. The MOE approach is consistent with current EPA guidance on risk assessment (USEPA 2003) and is appropriate for assessing the risks of PFOA.

The draft assessment uses serum PFOA level as the measure of dose for interspecies comparison rather than the traditional administered dose. As is widely recognized, use of an internal dose measure eliminates one of the major uncertainties in interspecies comparisons.

¹ I am a co-Founder of ENVIRON International Corporation, a health and environmental sciences consulting firm, and I have over 30 years of experience in toxicology and risk analysis. Prior to my consulting career, I spent 15 years with the Food and Drug Administration, for the last three years as Deputy Associate Commissioner for Science. I have served on over twenty Boards and Committees of the National Academy of Sciences and the Institute of Medicine, and serve as a Visiting Professor at Johns Hopkins University School of Public Health.

The use of such an internal dose measure is endorsed by the Agency's own latest guidance for risk assessment, both for carcinogens (USEPA 2003), and for non-carcinogens (USEPA 2002).

While comparisons of blood levels between humans and animals in this way is not typical for environmental chemicals, because of the rarity of such data for these types of chemicals, it is common for pharmaceuticals. For example, the procedure is commonly used for setting doses for carcinogenicity studies of pharmaceuticals (FDA 1995). When blood levels are available in humans and animals, especially when there are no complications due to species differences in metabolism of the chemical, internal dose comparisons are the preferred methodology because they reduce uncertainty in the overall risk assessment.

Because PFOA does not undergo metabolism, and other aspects of its pharmacokinetics are reasonably well understood, serum PFOA provides the most appropriate measure of dose for interspecies comparisons. I urge the SAB to fully support EPA's approach.

2. Uncertainty Factor for Interspecies Extrapolation

A major advantage of the use of an internal measure of dose, such as serum PFOA at steady state, is that it reduces or eliminates the uncertainty associated with the potential toxicokinetic differences between species, which comprise a portion of the interspecies uncertainty factor normally used in risk assessment.

The default interspecies uncertainty factor of 10 is considered to be comprised of two equal-sized portions: one addressing toxicokinetics, and one addressing toxicodynamics (Renwick and Lazarus 1998). Several considerations lead to the conclusion that the standard uncertainty factor for toxicokinetic aspect of interspecies extrapolation can justifiably be reduced for PFOA. It does not undergo metabolic conversion, so differences among species in metabolic handling do not need to be accounted for. Adequate data exist to provide a reasonable understanding of absorption, distribution, serum protein binding, and elimination in humans and experimental animals. Substantial data exist relating steady-state serum PFOA levels in several species of animals to various endpoints, and these effects occur in different species at similar serum PFOA levels. Thus, use of serum PFOA levels for estimation of MOEs reduces the uncertainty inherent in interspecies comparisons. Because toxicokinetic differences appear to be completely accommodated in the MOE approach, an overall uncertainty factor of 3 for interspecies extrapolation would be appropriate.

Such an approach is consistent with current EPA guidance for deriving RfCs and RfDs, and with EPA's practical application of these factors in deriving RfCs and RfDs for chemicals for which the toxicokinetics are understood.

- There are several examples of chemicals for which EPA has derived RfDs from animal data where the interspecies uncertainty factor is set at less than 10. These include at least two examples where toxicokinetics were explicitly considered in the RfD derivation:
 - Vinyl chloride, for which a physiologically based pharmacokinetic model was developed (<http://www.epa.gov/iris/subst/1001.htm>), and

- Acetone, for which the toxicokinetics were considered sufficiently similar among species to justify eliminating the uncertainty factor (<http://www.epa.gov/iris/subst/0128.htm>).
- All forty to fifty chemicals in EPA's IRIS database for which RfCs are derived from animal data incorporate a procedure for physiological scaling to derive a human equivalent dose (HED). The Agency then applies an uncertainty factor of 3.0 for interspecies scaling.

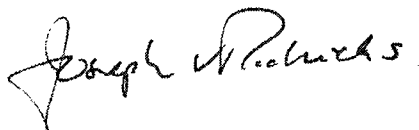
3. Use of NOAELs and LOAELs or Benchmark Dose

The draft assessment uses NOAELs and LOAELs for a variety of endpoints to assess the MOEs for human exposure. While there is a long history of using NOAELs and LOAELs for risk assessment, EPA has increasingly moved to the use of benchmark doses as points of departure (PODs) for this purpose. As EPA notes in its draft technical guidance document on the use of the benchmark dose procedure: "the benchmark dose (BMD) approach provides a more quantitative alternative to the first step in the dose-response assessment than the current NOAEL/LOAEL process for noncancer health effects, and is similar to that for determining the POD proposed for cancer endpoints" (USEPA 2000). They go on to note, "[t]he development of this approach has been pursued because of recognized limitations in the NOAEL/LOAEL approach" (USEPA 2000). NOAELs and LOAELs are highly dependent on sample size and dose selection, and may not represent a consistent level of response in different studies. Because of these limitations, EPA has increasingly adopted the benchmark dose procedure for many of its most recent assessments. The benchmark dose procedure systematically accounts for differences in study design, and provides a means to normalize such differences across studies that may affect identification of NOAELs and LOAELs.

That the PFOA data are amenable to the benchmark dose procedure is illustrated by the use of the procedure in the recently published risk assessment of PFOA by Butenhoff, et al. (2004). I urge the Agency to make use of benchmark dose methodology where feasible.

Thank you for your consideration of these comments.

Respectfully submitted,



Joseph V. Rodricks, Ph.D.

cc: Dr. Jennifer Seed, USEPA

References:

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- U.S. Environmental Protection Agency (USEPA). 2000. Benchmark Dose Technical Guidance Document. EPA/630/R-00/001, External Review Draft. Available at: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20871>
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